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T H E S I S

A STUDY OF THE PREPARATION OF CYCLIC AZO COMPOUNDS,

and

THE FINE STRUCTURE OF NAPHTHALENE,

submitted by

Norman Edward Perkins, B.Sc.

University of Alberta April 22, 1939.

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THESIS

A STUDY OF THE PREPARATION OF CYCLIC AZO COMPOUNDS,

and

THE FINE STRUCTURE OF NAPHTHALENE,

Submitted in partial fulfilment of the requirements for the degree of Master of Science.

By

Norman E. Perkins, B.Sc.
Under the direction of Dr. R.B. Sandin
In the Department of Chemistry

Time devoted to thesis work: 7.8 months out of 14.0 months devoted to M.Sc. work.

Time is proportioned on basis of 7.0 months for an academic year and 4 full courses representing one academic year's work.

EDMONTON, ALBERTA. April, 1939.

PART I

A STUDY OF THE PREPARATION OF CYCLIC AZO COMPOUNDS

Introduction

The purpose of this work was to study the preparation of some cyclic azo compounds corresponding to some extent in structure to certain of the fused carbocyclic systems known to be carcinogenic. The latter are believed to contain essentially the phenanthrene nucleus. Cancer producing compounds are known which have heterocyclic rings containing nitrogen, and it has been shown by Yoshida[6] and other workers that the simple azo dye o-aminoazotoluene produces cancer. Other simple azo compounds have been shown to cause proliferation of cells which does not necessarily reach a malignant stage.

As early as 1908 the azo dye Scarlet Red was used to promote healing of wounds since it causes proliferation of cells. These appeared histologically to resemble cancer but receded after a time. More recently, derivatives of o-aminoazotoluene have been used as salves to promote healing of wounds.[20]

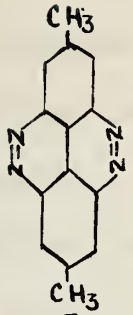
On the other hand Congo Red, which is also an azo dye, has been used to reduce or control

certain types of cancer. Another azo dye, Trypan Blue, has been used by one worker[18] to sensitize tumors to the action of X-rays, though it has also been shown[2] that it lowers the resistance of animals to the growth of tumors.

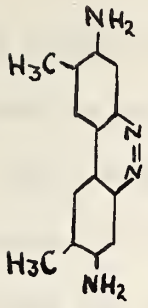
On this evidence it would seem that the effect of an azo compound may vary, from producing proliferation which may be malignant or benign, to causing reduction or at least retarding the growth of malignant cells.

It was thought, therefore, that if some cyclic azo compounds (of more complex structure than the simple ones already known and corresponding somewhat to fused carbocyclic cancer-producing compounds) were to be synthesized, some further information of value might be obtained.

Accordingly the synthesis of three compounds was attempted: I, corresponding to 1,2-benzpyrene (IV), which has been shown[7] to be the principal cancer-producing compound in coal tar; II and III, which are slightly more complex molecules based on the phenanthrene skeleton (V).



I



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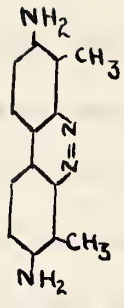
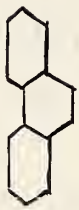


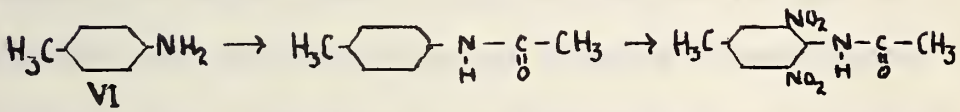
III

IV



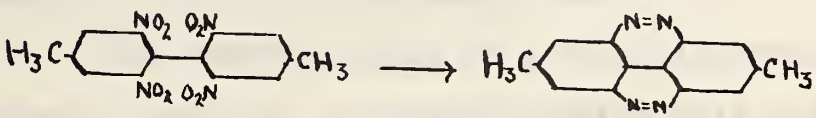
V

The steps involved in the preparation of the first compound were as follows:



VI

VII VIII



IX I

p-toluidine (VI) was acetylated, nitrated and the resulting compound was hydrolysed to give m-dinitro p-toluidine (VII). This was then diazotized to give p-iodo-m-dinitrotoluene (VIII). Two molecules of the latter were coupled by removing the two iodine atoms with copper bronze and 2,2′,6,6′-tetranitro-4,4′-dimethyldiphenyl was formed (IX). Reduction of this compound to give the cyclic azo compound (I) was unsuccessfully attempted.

Experimental Procedures

Aceto-p-toluidide.- It is necessary to protect an amine from oxidation before it can be nitrated and this is done by forming a derivative of the amine. In this case the amine was acetylated. Previous workers[9] in this laboratory had found that the most satisfactory method was to heat the amine at 100° for 20 minutes in glacial acetic acid with a slight excess of acetic anhydride.

Two hundred grams of p-toluidine was dissolved in 400 cc. of glacial acetic acid and 250 cc. of acetic anhydride was added. After 20 minutes heating at 100° the solution was diluted and allowed to come to room temperature. The precipitated

acetotoluidide was then filtered off, washed with dilute acetic acid and water, and dried; yield 258 g. The melting point (150.5°) indicated that the compound was sufficiently pure so that recrystallization prior to the next step was not necessary.

Nitration of aceto-p-toluidide.- Nitration was carried out by adding the dry acetotoluidide to fuming nitric acid which was kept cooled by immersion in an ice bath since a considerable amount of heat was liberated by the reaction. The solution was then diluted by pouring it into a large volume of ice water and the precipitate was rapidly filtered off. If the solution is allowed to warm up or to stand for any length of time the dinitroacetotoluidide is readily hydrolysed by the dilute nitric acid and the free amine is then acted on by the nitrous acid which is also present, the latter reaction resulting in the production of tarry substances. In order to facilitate rapid filtration and washing following dilution, only small quantities could be used. This necessitated a number of repetitions of the reaction in order to obtain a sufficient quantity of material.

Twenty grams of the acetotoluidide was stirred in small portions over 20 minutes into 200 cc.

of fuming nitric acid kept at about 10°C. The resulting solution was then poured into about 3 litres of ice water, the precipitate was rapidly filtered off and thoroughly washed with water. Allowing the temperature to rise or lengthening the time of nitration resulted in a considerable lowering of the yield as may be seen from the following table:

Time	17 min.	20 min.	25 min.	40 min.
Temp.	7°	10°	10°	15°
Yield	20 g.	18 g.	17 g.	9.5 g.

Some difficulty was experienced, in that, if the material was added too rapidly the low temperature required could not readily be maintained. Very little difference in quality was noticed in the various runs, the melting points varying from 183° to 187°.

Hydrolysis of the m-dinitroaceto-p-toluidide. - The dinitroacetotoluidide was hydrolysed by suspending it in 50% (by volume) sulfuric acid and heating on the steam bath until hydrolysis was complete. This generally took from four to eight hours. Completion of the reaction could be determined by the fact that, as hydrolysis proceeded,

the light yellow color of the acetyl compound was replaced by the deeper orange-yellow of the free amine.

The amine was then filtered off through glass wool, washed with 50% sulfuric acid, then with water, and finally air-dried.

Any mononitro compound which is formed remains in solution in the sulfuric acid and the dinitro compound is sufficiently insoluble that practically none is lost. In two hydrolyses the filtrate was diluted with an equal volume of water and it was found that a negligible amount of material precipitated.

The yield from 50 g. of dinitroacetotoluidide was 39 g. melting at 166°. This melting point again was sufficiently close to that of the pure compound (168°) that no recrystallization was necessary.

Preparation of p-iodo-m-dinitrotoluene. - Since the presence of two nitro groups in the ortho positions to the amino group tend to make it a very weak base, it is to be expected that ordinary methods of diazotization would be unsuitable. References may be found in the literature to methods of diazot-

ization suitable for weak amines. Two of these were tried.

In the first method, that of Schoutissen[19], sulfuric acid was used as the solvent.

Twenty grams of the dinitrotoluidine was dissolved in 80 cc. of concentrated sulfuric acid and the solution was cooled to 0°. A solution of sodium nitrite (7.5 g.) in concentrated sulfuric acid (40 cc.), also at 0°, was then stirred into the first solution. Sirupy phosphoric acid (80 cc.) was slowly added with vigorous stirring, the temperature being kept at 5°-10°. Stirring was continued for an hour and a half after all the phosphoric acid had been added to ensure complete reaction. The solution was then poured into 2 kg. of ice and water and filtered. Urea was added to remove any excess nitrous acid and then the solution was treated with a saturated solution of potassium iodide (17 g.). The mixture was warmed and treated with sodium bisulfite to remove free iodine. The crude material was filtered off and dried. The crude material weighed 21.5 g. and melted over a range 115°-130°.

In the method of Hodgson and Walker[14] 20 g. of the dinitro amine was dissolved in 240 cc. hot

glacial acetic acid and the solution was cooled rapidly in running cold water. The suspension was then added slowly to a cold solution of sodium nitrite in concentrated sulfuric acid (10% excess), the temperature being kept below 20°. Urea was added to remove excess nitrous acid and the solution was added to a saturated solution of 17 g. of potassium iodide in water. This mixture was allowed to stand for an hour, iodine was removed with sodium bisulfite and the mixture was poured into water.

The crude material which was filtered off weighed 25 g. and melted over the range 145°-148°.

On the basis of these results the second method was chosen.

After being recrystallized twice from glacial acetic acid the p-iodo-m-dinitrotoluene melted at 154.5°-155° and the yield of purified material was in most cases equal in weight to the starting material.

Preparation of 2,2',6,6'-tetranitro-4,4'-dimethyldiphenyl by means of the Ullmann reaction. - Ullmann[22] drew the following conclusions about the Ullmann reaction (heating aromatic halogeno-compounds with finely divided copper to form diaryls):

1. The order of reactivity of the halogen is I > Br > Cl.

2. The halogen is activated by the presence of an acidic group, particularly a nitro group, in the ortho position.

Hodgson and Elliott[13] state that diaryl formation by the Ullmann reaction appears to depend on the ability of the copper to form covalent cuprous iodide with the substituted iodine, since Cumming and Howie[8] found in their work on dinaphthyls that sodium did not effect condensation even in the case of ortho compounds. The Ullmann reaction thus differs from the Fittig reaction in that copper does not release one of its electrons to the carbon and so enable ionic iodine to separate, as sodium would do, whether acting as a metal or in sodium alkoxide. Consequently radical formation will depend upon the ease of detachment of neutral iodine from neutral carbon, e.g. $2RI + 2Cu \rightarrow 2R^{\cdot} + Cu_2I_2 \rightarrow R:R + Cu_2I_2$.

Due to the presence of two nitro groups ortho to the iodine (the combination most favorable to ease of reaction) it was thought advisable to slow the reaction down somewhat and this was accordingly done by using nitrobenzene as a solvent.

p-Iodo-m-dinitrotoluene (20 g.) was dissolved in 30 cc. of nitrobenzene and the solution was placed in a 150 cc. beaker suspended in an oil bath heated at 120°-130°. Activated copper bronze (20 g.) was added with stirring, in small quantities during an hour. After all the copper had been added the temperature was gradually raised to 200° and kept there for 30 minutes.

After cooling the mixture, several extractions were made with a mixture of nitrobenzene and benzene. The benzene was evaporated off and the tetranitroditolyl was precipitated by the addition of diluted ethyl alcohol (ca. 70%).

The tetranitroditolyl was recrystallized three times from benzene and melted at 249.5°. The purified yields averaged 65% of the theoretical yield.

The copper bronze was activated according to the method of Kleiderer and Adams[15]. Copper bronze (100 g.) was treated with 200 cc. of a 2% solution of iodine in acetone for 10 minutes, during which time the solution became decolorized. The copper was then filtered off, and washed with a solution of 10 cc. concentrated hydrochloric acid in

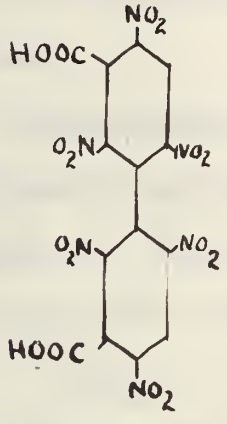
~~in~~ 100 cc. acetone until all the cuprous iodide had been washed out from the copper, and the filtrate was clear. The copper was then dried in a dessicator. The yield was 97 g.

Reduction of 2,2',6,6'-tetranitroditolyl. - It is usually considered that where two carbon atoms are joined by a single bond there is free rotation about that bond. In the case of the diphenyl molecule it has been found that in certain substituted diphenyls optically active isomers could be deparated. Christie and Kenner[5] put forward the theory, now generally accepted, that the two benzene rings in such a case were coaxial but noncoplanar. It was further postulated that, in order for the two nuclei to remain noncoplanar, the rotation must be restricted. Further work in this field has shown that substituents ortho to the diphenyl linkage may produce this restriction. Two conditions must be satisfied before this can occur:

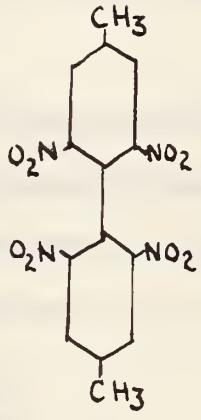
(a) There must be either three, or four substituents ortho to the diphenyl linkage.

(b) These substituents must be of sufficient influence on one another to effect the restriction.

This effect was explained by Mills[17] as being a purely mechanical hindrance, and this theory has been generally accepted, particularly as a result of the work of Adams. The latter has found[21] that the compound 3,3-dicarboxy-2,4,6,2,4,6-hexanitrodiphenyl (X) could be resolved into two stable, optically active isomers.



X



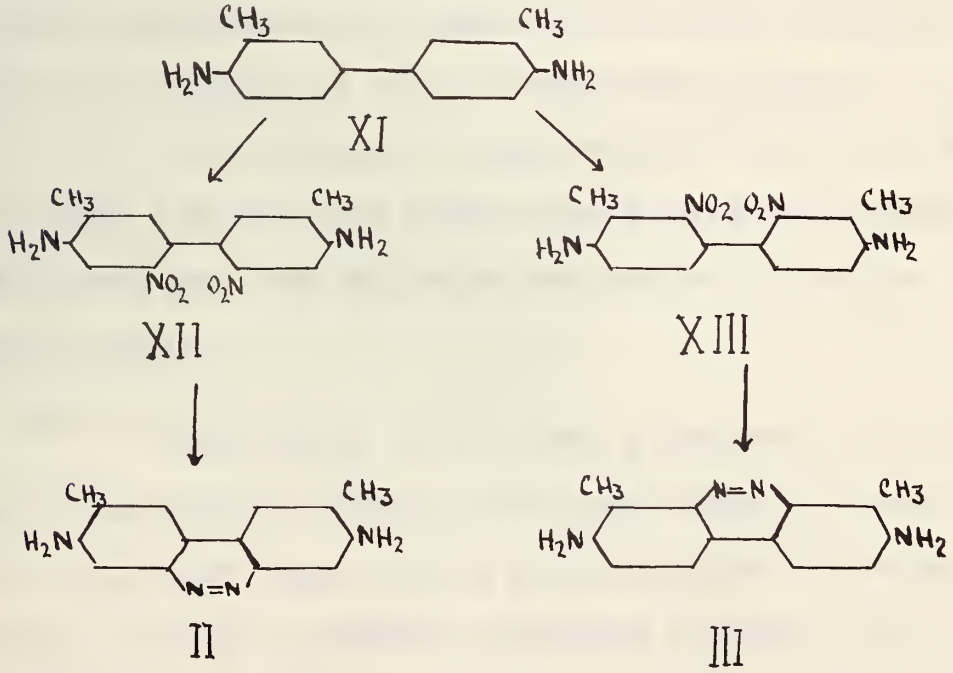
IX

This indicates that the two benzene rings are noncoplanar. Since, insofar as steric hindrance is concerned, 2,6,2′,6′-tetranitro-4,4′-dimethyldiphenyl (IX) is essentially the same as X, it should be noncoplanar.

If this is true, it is to be expected that it would be difficult to reduce this compound to the azo compound. Experimentally this was found to be so.

Attempts to produce an azo compound from the tetranitro compound using zinc and sodium hydroxide, sodium amalgam, and sodium stannite as reducing agents were unsuccessful. In each of these cases only the production of tarry substances could be detected, indicating probable reduction of the nitro groups to amino groups with destruction of the molecule. No intensification of color was observed at any time.

Preparation of 3,3′-dimethyl-4,4′-diamino-6,6′-azodiphenyl and 3,3′-dimethyl-4,4′-diamino-2,2′-azodiphenyl. - The steps involved in the preparation of these two compounds were as follows:



o-Tolidine (XI) is nitrated to produce isomers (XII) and (XIII) and these are reduced to produce the two azo compounds (II) and (III).

In the nitration of o-tolidine 5 dinitro isomers have been obtained. The isomer or isomers obtained may vary depending upon the procedure used and upon the particular derivative of o-tolidine which is chosen as a starting material.

Gerber[11] nitrated diacetyl-o-tolidine and obtained o-dinitro-o-tolidine. He also nitrated o-tolidine sulfate[10] to obtain m-dinitrotolidine (XII). Cain and Mickelthwait[4] repeated this work and also nitrated diphthalyl-o-tolidine. They found that in each case the product was largely compound XII but included at least three other isomers.

Since Gerber's publication[10] could not be obtained and Cain and Mickelthwait gave no detailed instructions, the following methods of nitration were tried:

A.

o-Tolidine (10 g.) was dissolved in 200 cc. of concentrated sulfuric acid kept cooled to about 10° in an ice bath, and to this solution was added 10 g. of finely powdered potassium nitrate. The mixture was stirred for ten minutes and allowed to

stand a further 2 hours with occasional stirring to permit complete solution and reaction of the potassium nitrate. It was then poured into 2 litres of ice water with rapid stirring. The acid was neutralized by the addition of ammonia and the solution was kept warm for some time to free the base completely, then the precipitated dinitro-tolidine (red) was filtered off. Incomplete neutralization or the use of sodium carbonate resulted in the precipitation of the yellow sulfate. The dry crude material weighed 14 g. and softened over a wide range of temperature beginning at 120° and melting finally at 170°.

The procedure was modified by diluting the solution at the end of 3 hours and filtering off the resulting precipitate. Liberation of the free base was then accomplished by suspending the washed precipitate in hot ammonia and heating till no yellow colored material remained. Results were approximately the same as before.

B.

Fifteen grams of o-tolidine was dissolved in 250 cc. of concentrated sulfuric acid, cooled as before, and 10 cc. of concentrated nitric acid was added slowly with stirring. After standing for 30

minutes the solution was diluted and the precipitate of dinitrotolidine sulfate was filtered off and neutralized with ammonia as before. The yield was 20.5 g. and melted over the range 175°-180°. This method was obviously superior because of the saving in time and increase in quality.

Attempts were made to purify the dinitrotolidine by recrystallization from benzene, but this was not satisfactory due to the long time taken for precipitation on cooling, and large losses in the mother-liquor. The material remaining in solution could not be recovered by evaporation of the solvent since tar was formed very readily. Crystallization from glacial acetic acid could be done easily, but the melting point did not rise very rapidly with successive recrystallizations.

The method of Cain and Mickelthwait[4] was tried and found to be successful. The dinitrotolidine was acetylated according to the previous method[9] and the acetyl compound was recrystallized once from glacial acetic acid with the addition of norite; melting point 279°.

The acetyl derivative was hydrolysed by heating on the water-bath with 50% by weight sulfuric

acid. The free base was obtained by the use of ammonia as before.

Recrystallization of the free base once from glacial acetic acid yielded m-dinitro-o-tolidine melting at 217°-218°. Nitration by this method was found to yield no appreciable quantity of any of the other isomers. Dilution of the acetic acid solutions and recrystallization of the resulting precipitates gave only further quantities of the same material.

In the hope of possibly duplicating the work of Cain and Mickelthwait, who obtained what were apparently quite small quantities (though they stated no yields) of the 2,2'-dinitro-o-tolidine, attempts were made to produce diphthalyl-o-tolidine. Hobbs[12] reports his synthesis of diphthalyl-o-tolidine very briefly as follows: "Das Condensationsproduct von Orthotolidin und Phtalsäureanhydrid krystallsirt aus Benzol in dunkelbraunen Nadeln, die bei 307° schmelzen."

Accordingly, five grams of o-tolidine was heated with 8 g. of phthalic anhydride at 175° in an oil bath with occasional stirring until no further condensation of water on the cover-glass could be

seen. On cooling a grayish mass remained. Almost no material could be extracted from this residue in boiling benzene, 95% alcohol, or glacial acetic acid.

The same procedure was repeated at 150° and at 200° with similar results. This procedure was therefore abandoned.

Reduction of 6,6'-dinitro-o-tolidine. - Reduction of the dinitro compound was carried out first according to the directions of Meyer[16] (who reported the synthesis of several cyclic azo compounds) but with little success. Intensification of color was noted but the material obtained proved, after recrystallization, to be the starting material. After increasing the amount of reducing agent, viz., sodium amalgam, and using a somewhat longer time for reduction, some of the desired material was obtained.

Eight grams of m-dinitro-o-tolidine was dissolved in 300 cc. of boiling alcohol. After the solution was cooled somewhat, 75 g. of 3% sodium amalgam was added and after standing for five minutes the solution was gradually warmed to a temperature slightly below the boiling point. The flask was kept at this temperature and a further 75 g. of amalgam was added at intervals over a

period of an hour, and the flask was then heated for a further 30 minutes.

At the end of this time the liquid was poured off from the mercury and filtered and diluted to 2 litres. The azo compound precipitated, was filtered off and washed with very dilute alcohol. It was recrystallized twice from alcohol and melted at 296° (Meyer: 276°). The yield was 25% of the theoretical.

Summary

1. An unsuccessful attempt has been made to prepare the cyclic azo compound of structure I.

2. The compound 3,3′-dimethyl-4,4′-diamino-6,6′-azodiphenyl (structure II) has been prepared.

3. An unsuccessful attempt has been made to prepare 3,3′-dimethyl-4,4′-diamino-2,2′-azodiphenyl (structure III).

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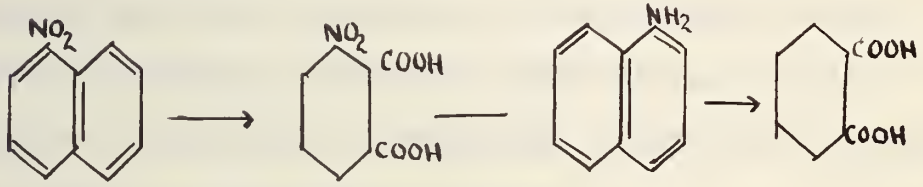
PART II

THE FINE STRUCTURE OF NAPHTHALENE

The structure of naphthalene presents a problem to which no definite answer can be made as yet, although most of the chemical evidence leaves room for only one solution.

When 1-nitronaphthalene is oxidized, 3-nitrophthalic acid is formed, whereas the oxidation of α-naphthylamine produces only phthalic acid.



Therefore, naphthalene consists of two fuzed benzene rings.

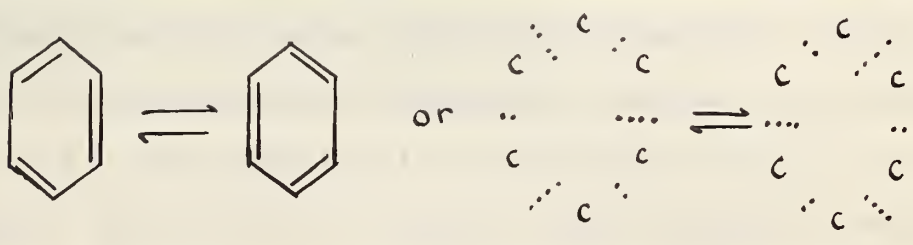
The fact that 2,6-dichloronaphthalene has no dipole moment indicates that the two rings in naphthalene are coplanar[9].

The course of catalytic hydrogenation of naphthalene has added to the evidence. With nickel catalysts naphthalene is converted first into tetralin and then, more slowly, into decalin.

Platinum catalysts usually give similar results, but Willstätter found that, with one particular type of catalyst containing very little oxygen, decalin was produced directly from naphthalene without the intermediate formation of tetralin. Zelinsky found, conversely, that decalin, on partial dehydrogenation at 300°, yielded naphthalene and unchanged decalin, but no tetralin. To the extent that such reactions can be relied upon, they afford some indication that naphthalene has a symmetrical structure.

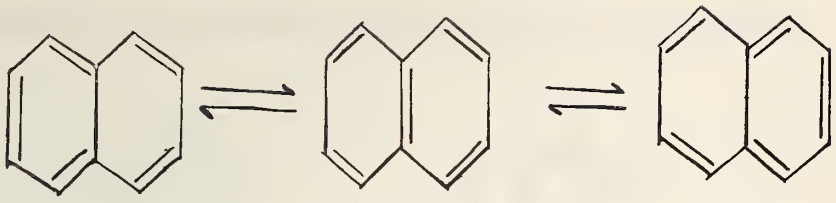
Attempts have been made to deduce the structure from quantum mechanics and from studies of various physical properties of naphthalene derivatives, including molecular refractions, dipole moments, dissociation constants, absorption spectra and Raman and infra-red apectra.

If resonance is considered to occur as it does in benzene,



three possible structures are suggested for

naphthalene.



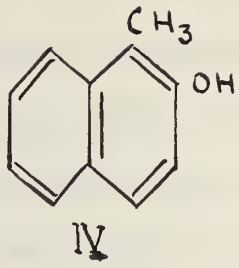
I II III

Some workers believe that an equilibrium between these three structures affords the most satisfactory explanation of the properties of naphthalene derivatives. However, most of the chemical evidence indicates that resonance is not involved, and favors structure II.

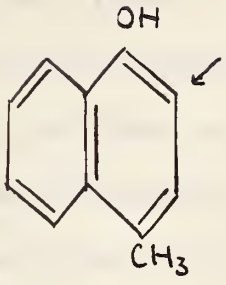
Chemical evidence rests chiefly on the reactivity of the 1-position, and the nonreactivity of the 3-position in 2 substituted compounds. This is explained as being due to the presence of a double bond between C_1 and C_2 and a single bond between C_2 and C_3.

The failure of the coupling reaction in certain specific cases favors the Erlenmeyer formula (II) for naphthalene. β-Naphthol couples at position 1, but if this position is blocked by a stable group (alkyl), as in IV, no coupling with diazotized amines occurs. A less stable group (carboxyl, halogen) at

the 1-position is displaced by the reagent, and in no case is the other ortho position attacked.



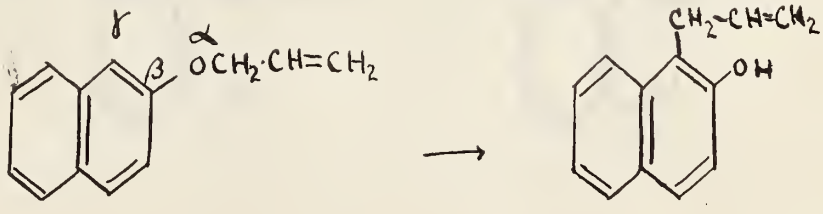
IV



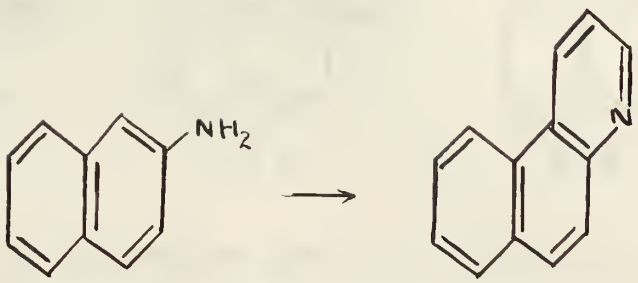
V

The failure of IV to react cannot be ascribed to the known lower degree of activity of the β-positions of naphthalene in comparison with the α-positions, for 4-methyl-1-naphthol (V) couples easily in the β-position, C_2. It is not merely a difference in the degree of reactivity which is involved, but a difference in kind, and the only plausible explanation is that the double bond, required in some way for the coupling, is available at the one position and not at the other.

The conversion of β-naphthyl allyl ether into 1-allyl-2-naphthol by the Claissen reaction represents a substitution by way of an intra-molecular rearrangement and it conforms to the same rules.

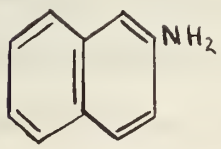


An alkyl substituent at the 1-position effectively prevents the rearrangement. If the reaction is considered to consist in an α,γ-shift, it may be said that the failure of a 1-substituted ether to rearrange shows that the carbon atom at position 3 cannot form the end of an α,γ-system, and hence that the double bond is incapable of migrating to the 2,3-position, even at the boiling point of the ether. The Skraup reaction of β-naphthylamine with glycerol, sulfuric acid, and an oxidizing agent may involve another kind of substitution, but it shows the same peculiarity. While β-naphthylamine forms a hetero ring extending to the 1-position, it does not form a ring extending to the 3-position, even when position 1 is blocked by a stable alkyl group as before. Apparently there is a general disposition for cyclization to occur in such a way that the new ring includes a double bond of the original ring system.

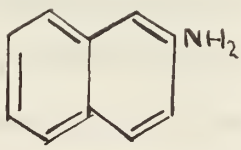


The extensive and varied evidence leaves little ground for questioning the conclusion that the two ortho positions of β-naphthol differ in kind. The only rational interpretation that has been given of this striking fact is, that the double and single bonds in a Kekule ring are fixed in the α,β - and β,β -positions, respectively.

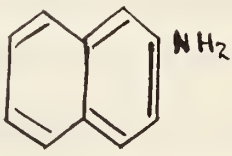
The establishment of the positions of the unsaturated centres in one part of the naphthalene molecule of course does not settle the problem of the complete bond structure. The facts cited above may be explained on the basis of either the symmetrical Erlenmeyer formula (VI) or the unsymmetrical structure (VIa), although in the latter case some additional assumption would be required regarding the failure of the substance to exist in the alternate unsymmetrical form (VIb).



VI



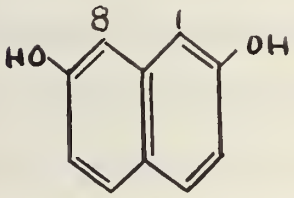
VI a



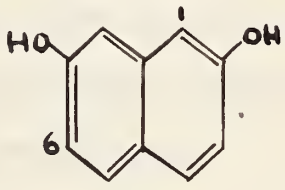
VI b

To determine the bond structure of the second ring, Fieser and Lothrop[6] extended to 2,6-

and 2,7-dihydroxynaphthalene methods of investigation employed successfully in the case of β-naphthol. If 2,7-dihydroxynaphthalene has the fixed symmetrical structure VII, it should be attacked by substituting agents at the two enolic ortho positions 1 and 8, but if it has the unsymmetrical structure VIIa the disubstitution should occur in the 1- and 6-positions.



VII

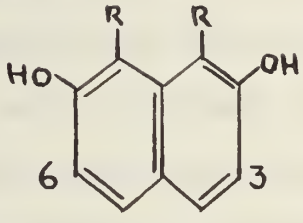


VIIa

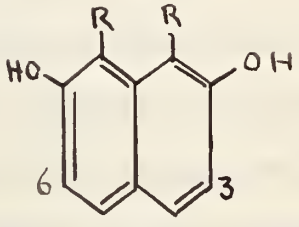
Actually, coupling occurs at the 1- and 8-positions, but although this observation supports formula VII it does not exclude the alternate formula. One can reconcile the observation with the unsymmetrical formula VIIa by supposing that the first substituent enters at C_1, and that the bonds then shift to the alternate unsymmetrical arrangement and provide an enolic group at C_7-C_8 for the entrance of the next azo group.

In order to settle the matter, Fieser and Lothrop investigated various 1,8-dialkyl derivatives

of 2,7-dihydroxynaphthalene. If such a compound has the symmetrical formula VIII, it should be incapable of ortho substitution in the free positions 3 and 6, but if it exists in the form VIIIa, or if it can tautomerize to this form having an available enolic ortho position at C_6, monosubstitution should be possible. Compounds of this type, as well as various 1,5-dialkyl-2,6-dihydroxynaphthalenes, were tested for phenolic properties with entirely negative results. They do not couple, even with particularly active diazo components, and their allyl ethers do not rearrange.



VIII

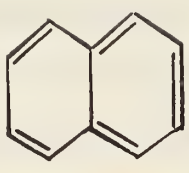


VIIIa

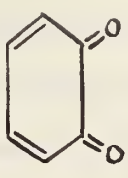
This evidence clearly indicates that the naphthols have the symmetrical structure of the Erlenmeyer formula and that the arrangement of the bonds represents a condition of considerable rigidits. A tautomerism to an unsymmetrical form does not appear to occur to any appreciable extent. Since there is no reason to suppose that naphthalene

itself differs from the naphthols, the evidence regarding the hydroxy compounds can be accepted as applying to the hydrocarbon.

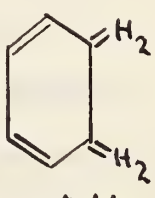
In considering the probable reason for naphthalene existing with the Erlenmeyer structure rather than the others, Thompson[15] has observed that, on the basis of the Mills-Nixon hypothesis, the unsymmetrical structure probably would be in a state of somewhat less strain than the symmetrical form and, consequently, that the strong tendency of the hydrocarbon to exist in the Erlenmeyer form is not due to steric factors. In all likelihood, naphthalene has little tendency to exist in the unsymmetrical form because one of its rings would then have to depart from the aromatic condition and acquire the bond structure of the highly reactive o-benzoquinone, or the character of the thermodynamically unstable 1,2-dihydrobenzene.



unstable



reactive



unstable

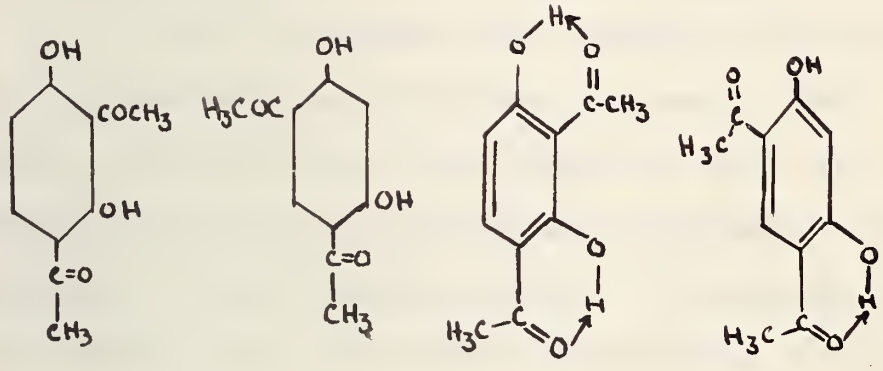
The resistance to the acquisition of quinonoid or

dihydride characteristics accounts for the lack of stability of this structure. In the Erlenmeyer formula neither ring is perhaps an entirely true benzenoid nucleus because the central bond is shared between the two rings and conjugated in different directions, but each approaches as nearly as possible the stable condition of an isolated benzene ring. The generalization of this important factor recognized by Fries has been designated by Fieser as Fries rule. This rule states that each aromatic ring of a polynuclear compound tends to assume the bond structure which most nearly approaches the condition of an isolated benzene ring.

Fries has based on the fixation of the bonds his explanation for the enhanced reactivity or unsaturation of naphthalene as compared with benzene. This reactivity, which is indicated by the occurrence of reactions under conditions such that benzene remains largely unaltered, is manifested particularly in the α-positions of the molecule, and the β-positions seem to exhibit only a slightly greater reactivity than the positions of the benzene ring.

The formation of a chelate ring may

determine the Kekule structure to a detectable extent. Baker[2], in studying the two diacetylresorcinols, 2,4-diacetylresorcinol (IX) and 4,6-diacetylresorcinol (X) found that these two compounds exhibited pronounced differences in physical and in some chemical properties.



IX X IXa Xa

Since both compounds contain two nuclear acetyl groups each adjacent to a hydroxyl group, it might be expected that they should closely resemble each other, both physically and chemically, and that the same degree of chelation should be possible to both. He found, however, by determinations of melting points, boiling points, solubility, volatility with steam, that IX is considerably more chelated than X.

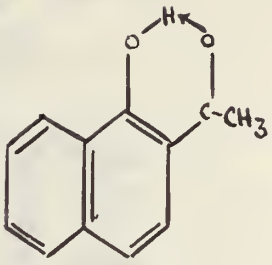
There can be little doubt that these

differences in behavior are to be ascribed to the possible double chelation of 2,4-diacetylresorcinol (IXa) and the single chelation only of 4,6-diacetylresorcinol (Xa), this, in its turn, depending on the necessity of the hydroxyl and the acetyl groups to be joined to mutually doubly linked carbon atoms of the benzene nucleus before chelation can occur.

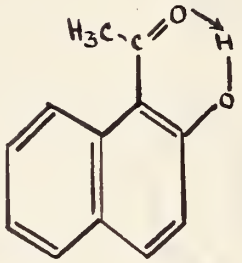
Baker[4] extended this work to a study of various o-hydroxyacetophenones and came to the general conclusion that the formation of a six-membered chelate ring containing coordinately linked hydrogen, as shown in IXa and Xa, is dependent upon the presence of a double bond between the carbon atoms bearing the hydroxyl and acetyl groups.

Using the same method, Baker[3] investigated the properties of the isomeric hydroxyacetylnaphthalenes (XI - XIV). As expected, XI and XII proved to be chelated, and XIV non-chelated, but XIII also proved to be chelated. The interpretation of this latter result may mean that chelation between the hydroxyl and acetyl group is sufficiently powerful to overcome the normal symmetrical arrangement of the naphthalene valencies, so that the molecule must assume the unsymmetrical distribution of the bonds

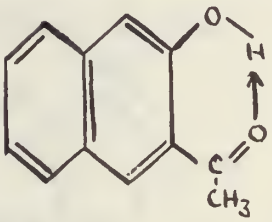
as shown in XIIIa, in which one of the rings is o-quinonoid. This is not indicated chemically.



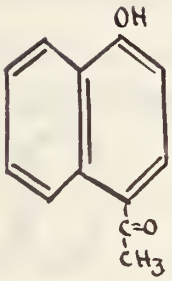
XI



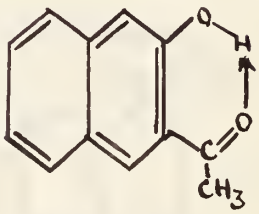
XII



XIII

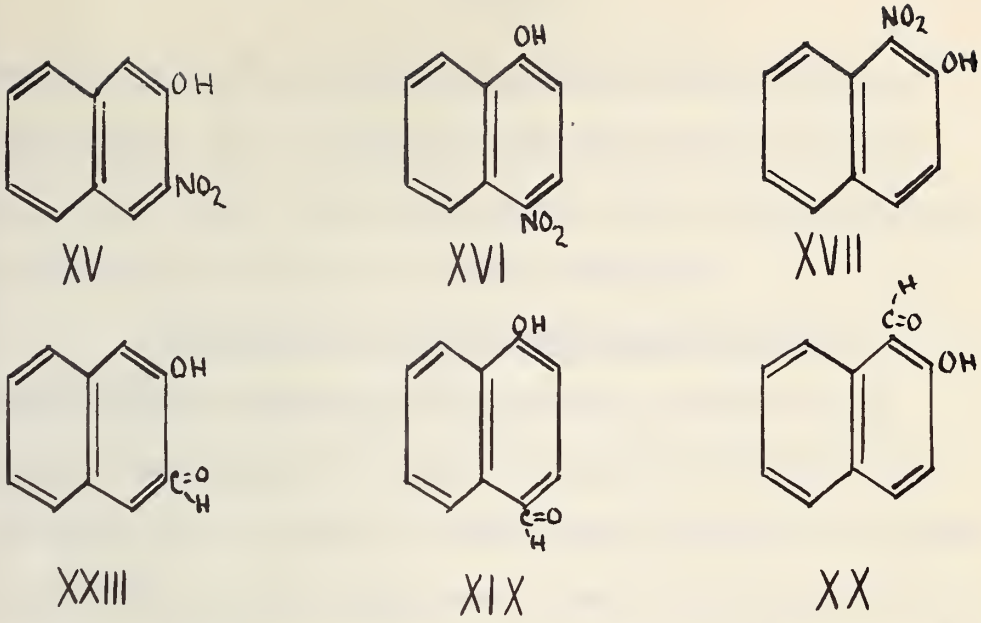


XIV

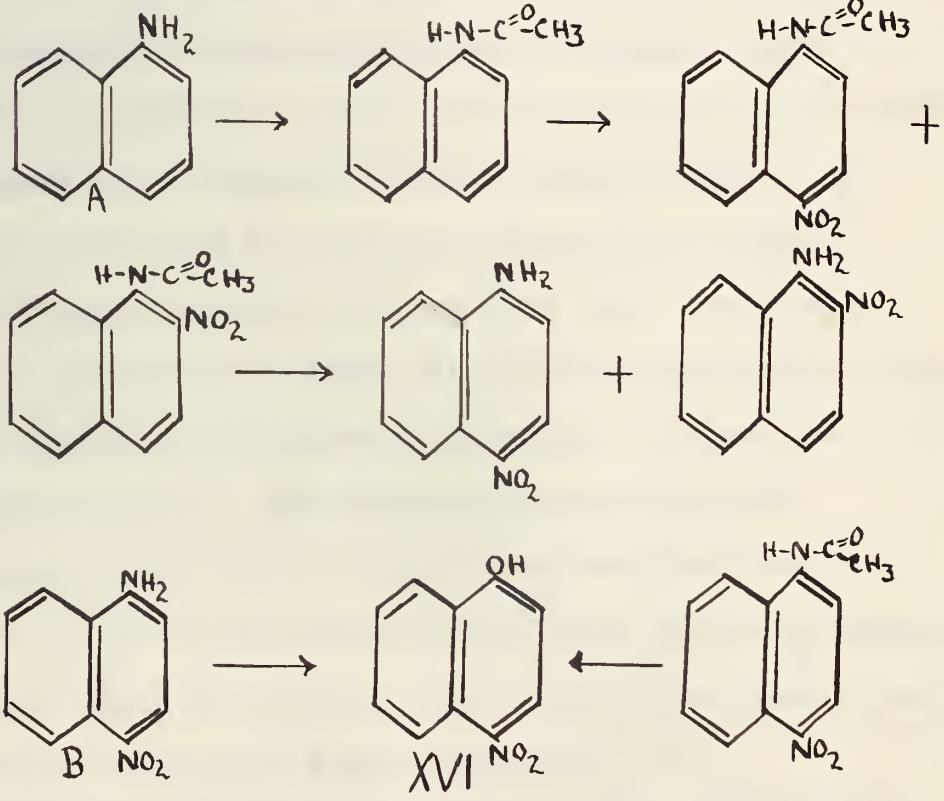


XIIIa

Other groups than the acetyl group are capable of forming chelate rings with the hydroxyl group and two of these are the nitro and the aldehyde groups. In the present work an attempt has been made to determine the extent of chelation in the nitro-naphthols (XV-XVII) and in the hydroxyaldehydes (XVIII-XX).



Preparation of 4-nitro-1-naphthol. - The reactions in this preparation were as follows:



α-Naphthylamine (A) was acetylated, and nitrated.

The resulting isomeric nitroacenaphthalides were hydrolysed, and 4-nitro-1-naphthylamine (B) was isolated. This was then heated with sodium hydroxide and 4-nitro-1-naphthol (XVI) resulted.

Nitration of aceto-α-naphthalide[5]. - Naphthylamine (Eastman's technical grade) 60 g., acetic anhydride, 55 cc., and glacial acetic acid, 400 cc., were heated to 100°, and maintained at that temperature for 20 minutes. The solution was cooled to about 10° by means of an ice bath. Twenty-nine cc. of concentrated acid was added dropwise, the low temperature being maintained as before. Some crystallization of the nitroacenaphthalides occurred during the nitration but the solution was quite clear when all the nitric acid had been added. Stirring was continued for some time after this. The container was then set in the ice-box over night, and crystallization was generally complete in less than 20 hours. The crystalline precipitate consisted of all the 2-nitro-acenaphthalide, and most of the 4-nitro-acenaphthalide, the remainder of which could be obtained by diluting the acetic acid filtrate from the mixed crystals.

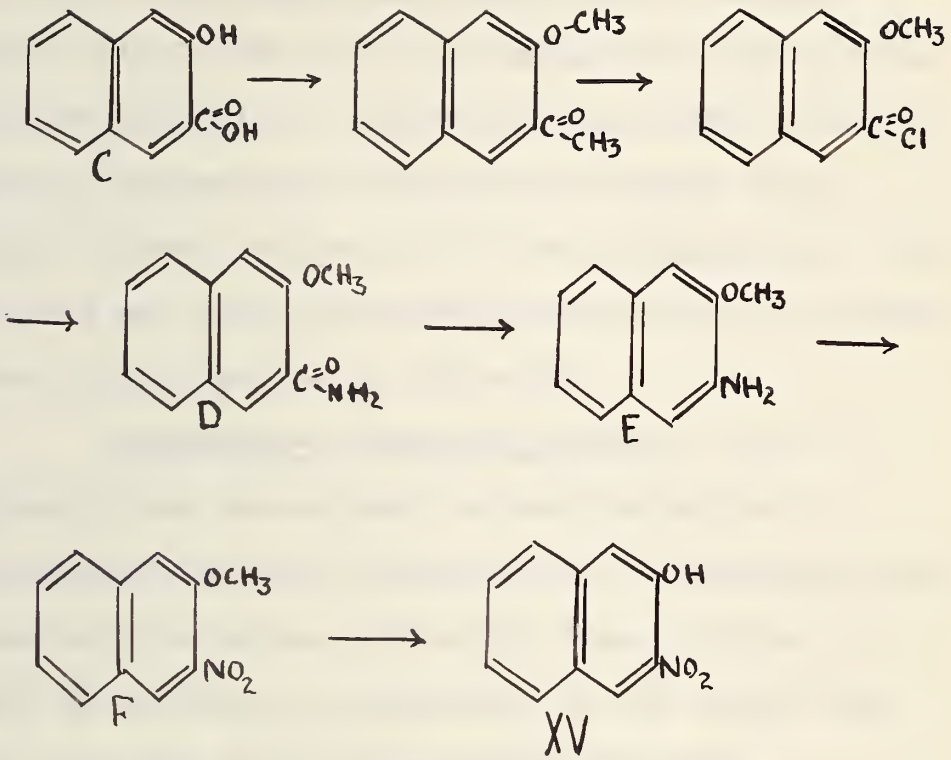
Hydrolysis of the mixed 2- and 4-nitro-

acenaphthalides. - Eighty grams of the mixed crystals (light yellow) 250 cc. of 95% ethanol, and 250 cc. of 50% by weight sulfuric acid were refluxed for 8 hours. The solution was then poured into 2 litres of distilled water, and the precipitated nitro-amines were filtered off.

Separation of the nitronaphthylamines. - Fifty grams of the mixed nitro-amines was dissolved in 500 cc. of glacial acetic acid, and the solution filtered while hot into 33 cc. of concentrated hydrochloric acid. On cooling, the hydrochloride of 4-nitronaphthylamine precipitated quantitatively, and 2-nitronaphthylamine remained in solution. The salt was filtered off and combined with the 4-nitro-acenaphthalide obtained previously by dilution of the acetic acid filtrate.

This mixture was then heated with 20% aqueous sodium hydroxide till no further ammonia was given off. The solution was then made slightly acid with hydrochloric acid and the 4-nitronaphthol was filtered off and dried. The crude yield was 50% of the theoretical yield. After recrystallizating four times from 25% alcohol with the addition of norite the product melted at 164.5°-165°.

Preparation of 2-nitro-3-naphthol. - The reactions in this preparation were as follows:



3-Hydroxy-2-naphthoic acid (C) was methylated and the product treated with thionyl chloride then ammonia, to give the acid amide of 3-methoxy-2-naphthoic acid (D). At the time of writing this point has been reached. The next step is a Hoffmann rearrangement to produce the amine (E). This is to be diazotized to produce the nitro compound (F) which on hydrolysis should give XV, the desired compound.

2-Methoxy-3-naphthoic acid.[3]- Ten grams

of 2-hydroxy-3-naphthoic dissolved in a mixture of acetone (100 cc.) and water (100 cc.), was warmed and shaken with successive small portions of methyl sulfate (in all 30 cc.) alternately with 20% aqueous potassium hydroxide. The solution was made strongly alkaline, heated for 2 hours on the water bath, cooled, diluted, and acidified with hydrochloric acid. The yield was 10 g. and after recrystallization from dilute alcohol melted at 131°-132°.

2-Methoxy-3-naphthoyl amide. - No difficulty was encountered in the production of 2-methoxy-3-naphthoyl chloride but a reasonable yield of the acid amide has not as yet been obtained. A number of methods of preparation of the amide have been tried but in all cases very low yields, accompanied by other products, as yet unidentified, have been obtained.

2-Methoxy-3-naphthoic acid was refluxed with thionyl chloride for one hour. After distilling off the excess thionyl chloride the product was treated with ammonia in several ways:

1. Ammonia gas was blown in by bubbling air through concentrated ammonia until the reaction seemed to be complete (no further ammonium chloride

fumes) and then concentrated ammonia was poured in. A further reaction took place with the evolution of more fumes and a rise in temperature.

2. Concentrated ammonia was added, in very small quantities at first (while cooling the flask on ice) and later in larger quantities until the reaction was complete.

3. Ammonia gas was passed in from boiling concentrated ammonia.

4. Ammonia gas, after being dried over calcium oxide, was passed in as in 1.

5. The acid chloride remaining was dissolved in anhydrous benzene and dry ammonia was passed in as before.

Following treatment with ammonia, water was added to dissolve ammonium chloride and the precipitate was filtered off, or in the case of (5), the benzene was evaporated. The resulting material was extracted with acetone to obtain the acid amide. In each case a small amount of the acid amide was obtained. Another compound, as yet unidentified, was obtained, in rather larger quantities, which could be recrystallized from alcohol. A considerable residue was left which was very slightly soluble in acetone,

soluble in dilute acetone and gave large transparent crystals on slow evaporation of the solvent.

Of the above methods the fifth gave the best results but from 10 g. of starting material the yield was under 1 g.

Next, both reactions were carried out in benzene by dissolving the methoxy acid in benzene and refluxing with a very small excess of thionyl chloride for 2-3 hours. Dry ammonia was passed in as before. The amount of the first unknown product was decreased and the amount of acid amide was increased to about 1.5 g. of crude material.

In the belief that impurities in the thionyl chloride were a possible source of side reactions, the material used (Eastman's Practical grade) was purified by distillation, first from quinoline and then from boiled linseed oil. The purified thionyl chloride was then used as in the last procedure but no significant difference in yield was found.

To verify the belief that the undesired reactions were taking place during the ammonolysis, the acid chloride was isolated and used in the pure state for ammonolysis.

Thirty grams of 3-methoxy-2-naphthoic acid

was refluxed with 70 cc. of thionyl chloride for 2 hours, and the product distilled, finally under reduced pressure. The acid chloride (18 g.), b.p. 201°/30 mm., melted at 53° (Baker and Carruthers: 57°). This material, dissolved in benzene, was treated with dry ammonia and gave 6.5 g. of material insoluble in water and on recrystallization from acetone gave 4 g. melting at 165°-167°. These results indicated very definitely that the trouble lay in the second step but due to lack of time this problem has not been solved.

1-Nitro-2-naphthol. - This material was purchased from Eastman Kodak Co. and melts at 103.8°-104.1°.

Preparation of 2-hydroxy-1-naphthaldehyde. - Hydroxy-aldehydes are most conveniently prepared by using the Gattermann reaction. This consists of saturating an anhydrous ether solution of a phenol and anhydrous hydrogen cyanide with dry hydrogen chloride, sometimes with the addition of anhydrous zinc chloride.

Adams and Levine[1] have modified this procedure so that the dangers of using hydrogen cyanide may be avoided. The modified method consists in using an

anhydrous ether solution of the phenol as before with the addition of zinc cyanide. Dry hydrogen chloride is then passed in which generates hydrogen cyanide and zinc chloride.

A 500 cc. wide mouthed Erlenmeyer flask was fitted with a stopper holding a mechanical stirrer fitted with a mercury seal, a reflux water condenser and an inlet tube, with wide mouth to prevent clogging from the precipitate, extending nearly to the bottom of the bottle. To this inlet tube was attached a safety bottle and to this a generator producing dry hydrogen chloride. To the top of the condenser was connected a tube leading into a wash bottle containing sulfuric acid; from this a tube was led to a safety bottle and from the bottle a tube to the surface of a sodium hydroxide solution.

Twenty grams of β-naphthol dissolved in 175 cc. of anhydrous ether was placed in the reaction flask. Zinc cyanide (25 g.) was then added. The mechanical stirrer was started and dry hydrogen chloride was passed in rapidly. The zinc cyanide gradually disappeared, sometimes leaving a milky solution (probably due to suspended sodium chloride) and as more and more hydrogen chloride was dissolved

the imide-hydrochloride condensation product began to separate as a thick yellow oil. In about 30 minutes this oil turned to a solid. At the end of 1.5 hours the ether was usually saturated with hydrogen chloride. When this point was reached the stream of gas was passed in more slowly and stirring was continued for 30 minutes longer to be certain that all the naphthol had reacted.

The ether was then decanted from the solid material and the imide-hydrochloride decomposed with 15% alcohol. The aldehyde was recrystallized a number of times from very dilute alcohol with the addition of norite until it had a constant melting point of 82.8°-83.4°.

At first, attempts were made to decompose the imide-hydrochloride using water but this resulted in the production of a red oil which could not be crystallized readily and had a very low melting point. Fairly dilute alcohol (about 15%) was found to be necessary for recrystallization in order to successfully purify the compound.

The yield of purified material was approximately 50% of the theoretical yield.

Preparation of 4-hydroxy-1-naphthaldehyde. - α-Naphthol was the initial material. The procedure and quantities were the same in this case as in the previous one. The imide-hydrochloride obtained was again hydrolysed using dilute alcohol and it was recrystallized as above; melting point 179.0°-179.5°.

The zinc cyanide for these reactions was prepared according to the directions of Adams and Levine[1]. To 107 g. of technical sodium cyanide dissolved in 135 cc. of water was added magnesium chloride solution until no more precipitate of magnesium hydroxide and carbonate formed. The precipitate was filtered off immediately and the filtrate added at once to 275 g. of zinc chloride dissolved in as small an amount as possible of 50% alcohol. The zinc cyanide precipitated and was filtered off. It was washed on the filter paper with alcohol, then with ether and dried over sodium hydroxide in a dessicator.

Adams and Levine[1] state that the impurities still present in the zinc cyanide do not interfere with the Gattermann reaction. Richard and Arnold[13], however, have stated they believe that it is necessary to have chlorides present as impurities for good results.

Detection of Chelation. - A number of methods are available for detection of chelation. Many of these consist in measuring simple physical properties. The principal factor upon which these methods depend is that if the hydroxyl group is used for forming a chelate ring it is not available for association, nor can its presence as a free group be detected by physical measurements. In other words, the hydrogen atom has a maximum coordinate number 2.

The most convincing demonstration of the existance of chelate rings involving 2-covalent hydrogen has come from infra-red spectroscopy. Hilbert, Wulf, Hendricks and Liddel[10] have found that absorption in the region characteristic of the hydroxyl group (6200-7500 cm^{-1}) is absent for a large number of compounds having configurations that would favor formation of a chelate ring containing the hydrogen bond O-H←O or O-H←N. The characteristic hydroxyl absorption was retained in related compounds where the constitutions or configurations excluded the formation of such bonds.

Information may be obtained as to the existance of chelation by the determination of

several physical properties:

1. Of two isomers the chelated one usually has the lower melting point.

2. The chelated isomer (i.e. the non-associated one) is usually more soluble in non-associated solvents (benzene)than it is in associated solvents (water) and vice versa.

3. The chelated isomer is easily volatile with steam, while the unchelated one is less so or non-volatile depending on its solubility in water and its boiling point.

4. The boiling point of the associated isomer is usually found to be abnormally high when other members of the series and similar compounds are considered.

5. Determination under water of the melting points of the two compounds will show that the melting point of the chelated compound is depressed a very small amount compared to that of the unchelated compound.

6. The molecular weight of a chelated compound, as determined cryoscopically, will be close to the theoretical molecular weight and will not increase much as the concentration of the solute is

increased. On the other hand, if the solute is able to associate, then the molecular weight will not only be larger than the theoretical molecular weight, but it will increase relatively rapidly with increasing concentration of the solute.

The last method is the one used in this investigation. It is customary in such determinations to use a solvent which is not associated and which can not associate with the solute. If a solvent is used which can associate with the solute it is found that the molecular weight, as measured cryoscopically, rises less with concentration than it otherwise would.

In the case of the six compounds to be used here, benzene did not possess sufficient solvent power to be used. Other non-associating solvents were tried (bromoform, cyclobenzene, xylene and naphthalene). The only one of these which would dissolve a sufficient amount of material in each case was naphthalene, but this had to be abandoned as a solvent because the losses by sublimation were considerable and could not readily be controlled. Nitrobenzene was finally found to be the only solvent available and this was used despite the fact that it

could associate with the solute. Even then, in the case of compounds XV and XVIII, only a limited amount could be dissolved.

The determinations of molecular weights were carried out in the manner recommended by Reilly and Rae[12]. A weighed quantity of the solvent (about 25 g. accurately to 0.01 g.) is placed in a large test tube and the stopper, with a Beckmann thermometer and glass stirrer, is fitted. This tube is placed in a wider tube, which serves as an air-jacket, and this is placed in an ice and water bath contained in a battery jar. The freezing bath must have a temperature of not more than 3° lower than the freezing-point of the solvent. This was effected by keeping the level of the ice not lower than half the length of the air-jacket and controlling the temperature of the water below it by varying the rate of stirring. The bulb of the thermometer is placed about half-way down in the solute. An approximate value of the freezing-point is first obtained. The tubes having been placed as above, the solvent is slowly stirred at the rate of about 1 stroke per second; when the solid begins to separate the rate of stirring is increased for a time and then the slower rate is

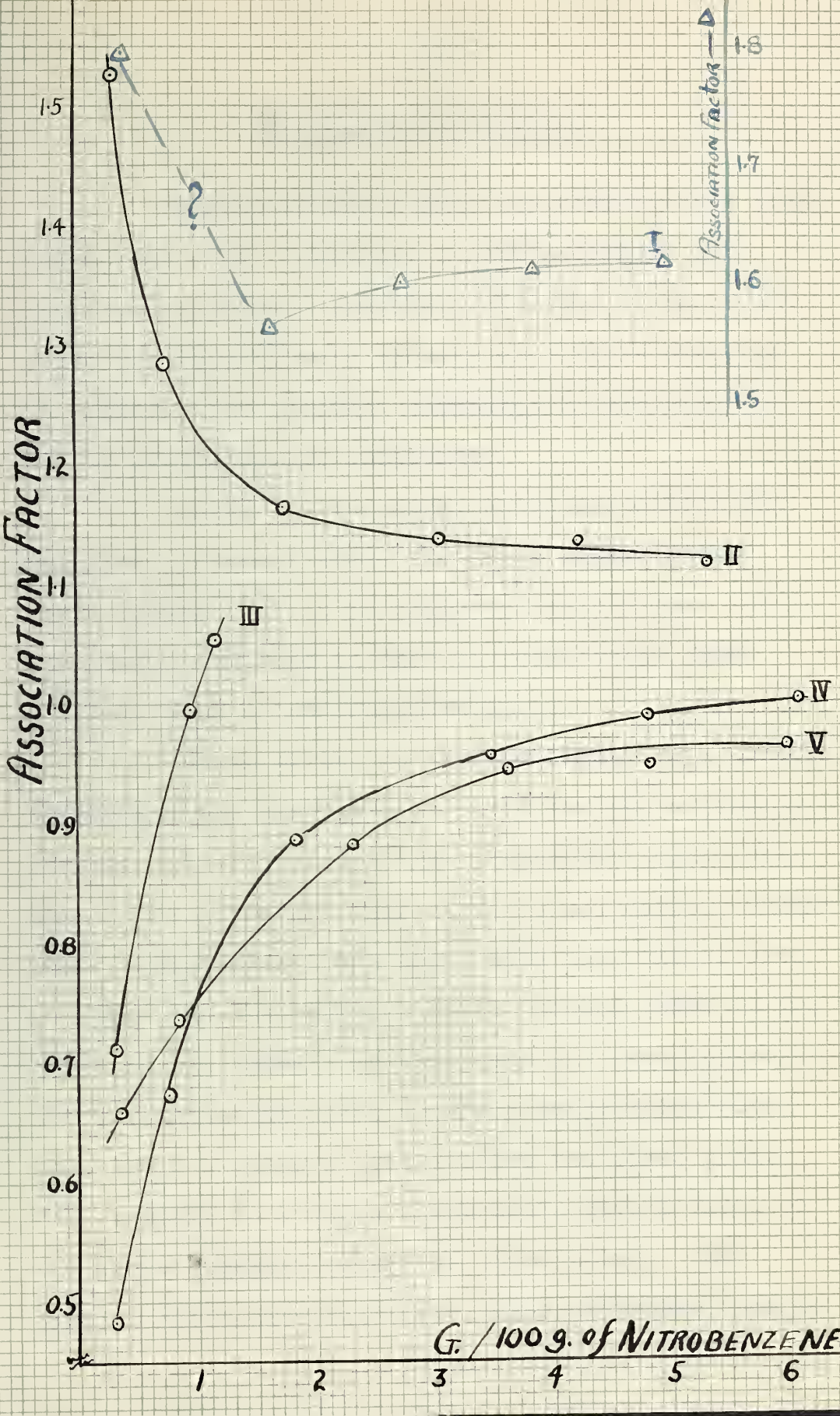
resumed. The mercury rises when the faster rate of stirring takes place, and the highest point to which it rises is taken as the freezing-point. The inner tube is now removed and allowed to warm in the air with vigorous stirring. When all the solid has disappeared, the tube is at once replaced in the air-jacket and slowly stirred until the temperature falls 0.1°C below the freezing-point. Freezing is then induced by rapid stirring, and as soon as the temperature begins to rise, slow stirring is resumed, the highest point to which the mercury rises being observed, while tapping the thermometer. This procedure is repeated until three readings, agreeing to 0.002°C., are obtained. Supercooling is kept as small as possible and is kept from exceeding 0.5° by the addition of a very small crystal of the solvent, if necessary. The solid is weighed in the form of a pellet and introduced, sufficient being used to produce a lowering greater than 0.1°. The freezing-point is then determined in the manner already described. Several values are obtained at increasing concentrations. The same Beckmann thermometer was used throughout and all nitrobenzene used was from the same source.

Molecular weights were calculated according to the usual formula $\frac{100k \times w}{\Delta t \times W} = M$, where the cryoscopic constant for nitrobenzene[12], k = 70.5; and Δt is the lowering of the freezing-point produced in W g. of the solvent by w g. of solute. The results are tabulated below and are shown in graphic form by plotting the concentration of solute (in grams in 100 g. of solvent) on the horizontal axis against the association factor on the vertical axis. The association factor is obtained by dividing the molecular weight, as determined, by the theoretical molecular weight.

Figures in parenthesis indicate the normal molecular weight: M is the apparent molecular weight. Concentrations are given as g./100 g. of nitrobenzene; a is the association factor.

	Concn.	M.	a.
2-hydroxy-1-naphthaldehyde (172) (Curve IV)	0.33	82.7	0.481
	0.75	115.7	0.673
	1.83	152.6	0.887
	3.50	164.6	0.957
	4.80	170.2	0.989
	6.08	174.8	1.016
4-hydroxy-1-naphthaldehyde (172) (Curve III)	0.31	122.3	0.711
	0.95	171.1	0.945
	1.18*	181.0	1.052
1-nitro-2-naphthol (189) (Curve V)	0.37	124.5	0.659
	0.85	139.3	0.737
	2.31	166.6	0.881
	3.61	178.6	0.945
	4.81	179.4	0.949
	5.99	182.1	0.963
4-nitro-1-naphthol (189) (Curve II)	0.32	288.5	1.527
	0.75	242.8	1.284
	1.75	219.8	1.163
	3.04	215.3	1.139
	4.23	214.6	1.136
	5.33	211.2	1.118
p-nitrophenol (139) (Curve I)	0.40	249.6	1.796
	0.88	?	?
	1.64	217.6	1.565
	2.74	222.5	1.601
	3.86	224.2	1.613
	4.97	225.1	1.619

* The substance was not sufficiently soluble for measurements to be made at higher concentrations.


Association factor
1.8
1.7
1.6
1.5
?
I
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
II
III
IV
V
Association Factor
G. / 100 g. of Nitrobenzene
1
2
3
4
5
6

Discussion of Results

Curves IV and V show quite definitely that these compounds (2-hydroxy-1-naphthaldehyde and 1-nitro-2-naphthol) are chelated. The slope of the curve corresponds very closely with those obtained by Hunter[11] for chelated compounds in the study of a number of diazoamino compounds.

Curve III is rather short for making any definite statement about its final shape, but it would appear that it is characteristic of an associated compound in that it crosses the line a = 1 at such a low concentration.

Curve II is, to say the least, very unusual. No explanation has yet been found for the extremely strange behavior of 4-nitro-1-naphthol, though the author believes that this curve is not quite a unique one. p-Nitrophenol was tried with the results seen in Curve I. The position of the second point in the curve is not known. In this case the freezing-point, after fluctuating about a narrow range which would have given a value a little above the first point, fell rapidly to a value which would give a value on the curve somewhat below the third point. No similar difficulty was experienced elsewhere, and, in

most cases, closely checking values were readily obtained. There was not sufficient time to do duplicate determinations for these compounds and the author would like to suggest that if possible, further examination of the behavior of these compounds be made. Measurements of the molecular weights of other para-nitro compounds in the naphthol and phenol series should assist in the solution of this question. It is felt that it is not likely that the reversal of the curve is due to experimental error, particularly in view of the fact that the maximum spread of values obtained for any one freezing-point is considerably smaller than the difference necessary to invert the curves I and II.

Further evidence that there is some radical difference in the behavior of 4-nitro-1-naphthol is the extent of color intensification noted in the solution. At the final concentration, the solution was a dark brownish-yellow which, although clear, could only be seen through with a strong light.

In the case of 4-hydroxy-1-naphthaldehyde, the solution was rather darker than that of 2-hydroxy-1-naphthaldehyde despite the fact that, of the two crystalline substances, the ortho compound

has the most color. This was taken as additional evidence that association occurred to a considerable extent in the para compounds.

In the course of this work some further evidence has been obtained regarding the compounds used. In the preparation of 2-hydroxy-1-naphthaldehyde, the aldehyde group has two ortho positions apparently open to it (α and β) but it has not been found at any time to enter into the β-position during a Gattermann reaction. In the case of 4-hydroxy-1-naphthaldehyde, this is the principal product, but in some cases the crude product is colored green by the presence of small amounts of the 1-hydroxy-2-naphthaldehyde which indicates that the β-position is not completely unreactive.

Evidence obtained here to show that there is a double bond in the α , β -position in naphthols does not of course exclude the possibility of tautomerism to a configuration having a double bond in the β , β -position. In order to exclude this possibility it will be necessary to continue the work by completing the synthesis of the two β , β compounds and measuring their molecular weights in a similar manner.

In this connection, the very fact that β,β compounds are so difficult to synthesize and are usually only made by very circuitous methods is an indication in itself that there is not a double bond in this position.

Summary

The compounds of formulae XVI, XVII, XIX and XX have been prepared and their molecular weights in nitrobenzene have been measured over a range of concentrations. From these measurements it has been shown that compounds XVII and XX have a double bond in the α,β-position, thus adding, possibly, further evidence to that which leads to the belief that the double bonds in naphthalene are fixed in the positions indicated by the Erlenmeyer formula.

ACKNOWLEDGEMENT

The author wishes to express his appreciation to Mr. Gordon R. Finlay for financial assistance during the course of this work.

Sincere gratitude is due to Dr. R.B. Sandin for the advice, assistance and encouragement which made this work possible.

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B29746